The inventions mentioned below disclose GH-RH analogs with antagonistic or agonistic properties on the pituitary receptors for GH-RH. However it was not reported and not investigated whether these analogs could exert direct effects on tumor cells.

US Patent 4,659,693 discloses GH-RH antagonistic analogs which contain certain N,N'-dialkyl-omega-guanidino alpha-amino acyl residues in position 2 of the GH-RH(1-29) sequence.

structure of hGH-RH by modifying its amino acid sequence. These earlier attempts include: replacing Tyr^1, Ala^2, Asp^3 or Asn^8 with their D-isomers; replacing Asn^8 with L- or D-Ser, D-Arg, Asn, Thr, Gln or D-Lys; replacing Ser^9 with Ala to enhance amphiphilicity of the region; and replacing Gly^{15} with Ala or Aib. When R^2 in the analogs is D-Arg, and R^8, R^9, and R^{15} are substituted as indicated above, antagonistic activity is said to result. These antagonistic peptides are said to be suitable for administration as pharmaceutical compositions to treat conditions associated with excessive levels of GH, e.g., acromegaly.

The antagonistic activity of the hGH-RH analogue "$[Ser^9\text{-psi}[CH_2\text{-NH}]\text{-}Tyr^{10}]$hGH-RH(1-29)" of US Patent 5,084,555 was said to result from the pseudopeptide bond (i.e., a peptide bond reduced to a $[CH_2\text{-NH}]$ linkage) between the R^8 and R^{10} residues. However, the antagonistic properties of $[Ser^9\text{-psi}[CH_2\text{-NH}]\text{-}Tyr^{10}]$hGH-RH(1-29) were said to be inferior to the standard antagonist, $[N\text{-Ac-}Tyr^1, D\text{-}Arg^2]$hGH-RH(1-29)-$NH_2$.

US Patent 5,550,212, US Patent 5,942,489, and US Patent 6,057,422, assigned to the same assignee as the present application, disclose analogs of hGH-RH(1-29)NH_2 said to have enhanced antagonistic properties and prolonged duration of action regarding the inhibition of GH-RH-evoked GH release. These properties are believed to result from replacement of various amino acids and acylation with aromatic or nonpolar acids at the N-terminus of GH-RH(1-29)NH_2. The tumor inhibitory properties of antagonists featured in US Patent 5,942,489 and US Patent 6,057,422 have been demonstrated by using nude mice bearing xenografts of experimental human cancer models. It is noted that in US Patent 5,550,212, and in US Patent 5,942,489, R^9 is always Ser, while R^{11} and R^{20} can be either Arg, D-Arg, or Cit. In the case of US Patent 6,057,422, R^9 can be either Arg, Har, Lys, Orn, D-Arg, D-Har, D-Lys, D-Orn, Cit, Nle, Tyr(Me), Ser, Ala, or Aib, while R^{11} and R^{20} are always Arg.

SUMMARY OF THE INVENTION

There is provided a novel series of synthetic analogs of hGH-RH(1-29)NH_2 and hGH-[illegible]. These analogs inhibit the release of growth hormone from the pituitary in mammals [illegible] cancers through a direct effect on the cancer cells. The